SUPPORT FOR THE AMENDMENTS

Applicants have amended Claim 1 to recite that the disease caused by mitochondrial dysfunction is MELAS and the composition further comprises at least one more mitochondrial adjuvant selected from the group consisting of glucose, fructose, mannose, galactose, sucrose, maltose, lactose, starch, citric acid, aconitic acid, isocitric acid, α-ketoglutaric acid, succinic acid, fumaric acid, malic acid, oxaloacetic acid, 2-keto-4-hydroxypropanol, 2,4-dihydroxybutanol, 2-keto-4-hydroxybutanol, 2,4-dihydroxybutyric acid, 2-keto-4-hydroxybutyric acid, aspartates, monoalkyl oxaloacetates, dialkyl oxaloacetates, mono- or di-alkyl citrates, aconitates, isocitrates, α-ketoglutarates, succinates, fumarates, malates, oxaloacetates, Vitamin B_1, Vitamin B_2, Vitamin B_6, Vitamin B_{12}, Vitamin C, Vitamin A, Vitamin D, Vitamin E, Vitamin K, Vitamin H, folic acid, pantothenic acids, L-isoleucine, L-leucine, L-valine, L-lysine, L-methionine, L-phenylalanine, L-threonine, L-tryptophan, L-alanine, L-arginine, L-aspartic acid, L-cysteine, L-glutamic acid, L-histidine, L-proline, L-serine, L-tyrosine, glycine, an inorganic calcium salt, an inorganic sodium salt, an inorganic potassium salt, an inorganic magnesium salt, an inorganic chlorine salt, an inorganic phosphorus salt, an inorganic zinc salt, an inorganic iron salt, an inorganic manganese salt, an inorganic copper salt, an inorganic chromium salt, an inorganic molybdenum salt, an inorganic selenium salt, an inorganic fluorine salt, an inorganic iodine salt, an organic calcium salt, an organic sodium salt, an organic potassium salt, an organic magnesium salt, an organic chlorine salt, an organic phosphorus salt, an organic zinc salt, an organic iron salt, an organic manganese salt, an organic copper salt, an organic chromium salt, an organic molybdenum salt, an organic selenium salt, an organic fluorine salt, and an organic iodine salt. Support for amended Claim 1 can be found on page 2, lines 4-5, and on page 11, line 1, to page 13, line 8, of the specification and Claim 5, as previously presented.

Claims 7 and 14 have been amended to recite that the disease caused by mitochondrial dysfunction is MELAS. Support for these amendments can be found on page 2, lines 4-5, of the specification.

Claims 11 and 18 have been amended to recite that the another mitochondrial function adjuvant is selected from the group consisting of glucose, fructose, mannose, galactose, sucrose, maltose, lactose, starch, citric acid, aconitic acid, isocitric acid, α-ketoglutaric acid, succinic acid, fumaric acid, malic acid, oxaloacetic acid, 2-keto-4-hydroxypropanol, 2,4-dihydroxybutanol, 2-keto-4-hydroxybutanol, 2,4-dihydroxybutyric acid, 2-keto-4-hydroxybutyric acid, aspartates, monoalkyl oxaloacetates, dialkyl oxaloacetates, mono- or di-alkyl citrates, aconitates, isocitrates, α-ketoglutarates, succinates, fumarates, malates, oxaloacetates, Vitamin B_1, Vitamin B_2, Vitamin B_6, Vitamin B_{12}, Vitamin C, Vitamin A, Vitamin D, Vitamin E, Vitamin K, Vitamin H, folic acid, pantothenic acids, L-isoleucine, L-leucine, L-valine, L-lysine, L-methionine, L-phenylalanine, L-threonine, L-tryptophan, L-alanine, L-arginine, L-aspartic acid, L-cysteine, L-glutamic acid, L-histidine, L-proline, L-serine, L-tyrosine, glycine, an inorganic calcium salt, an inorganic sodium salt, an inorganic potassium salt, an inorganic magnesium salt, an inorganic chlorine salt, an inorganic phosphorus salt, an inorganic zinc salt, an inorganic iron salt, an inorganic manganese salt, an inorganic copper salt, an inorganic chromium salt, an inorganic molybdenum salt, an inorganic selenium salt, an inorganic fluorine salt, an inorganic iodine salt, an organic calcium salt, an organic sodium salt, an organic potassium salt, an organic magnesium salt, an organic chlorine salt, an organic phosphorus salt, an organic zinc salt, an organic iron salt, an organic manganese salt, an organic copper salt, an organic chromium salt, an organic molybdenum salt, an organic selenium salt, an organic fluorine salt, and an organic iodine

salt. Support for amended Claims 11 and 18 can be found on page 11, line 1, to page 13, line 8, of the specification.

No new matter has been added. Claims 1-4, 6-11, 13-18, and 20 are active in this application.

REMARKS/ARGUMENTS

At the outset, Applicants wish to thank Examiner Webb for indicating that Claims 5, 11, and 18 are free of the prior art. Applicants respectfully submit that, in view of the present amendments and remarks, all of the pending claims are fully patentable.

Present Claims 1-4 and 6 relate to compositions for treating the expression of clinical symptoms in a disease caused by mitochondrial dysfunction, wherein said composition is an orally administrable composition comprising L-arginine as an active ingredient and a nitric oxide-releasing agent selected from the group consisting of glyceryl trinitrate, isosorbide mononitrate, isosorbide dinitrate, molsidomine, and S-nitroso-N-acetyl-DL-penicillamine,

wherein said disease caused by mitochondrial dysfunction is MELAS and

wherein said composition further comprises at least one more mitochondrial adjuvant selected from the group consisting of glucose, fructose, mannose, galactose, sucrose, maltose, lactose, starch, citric acid, aconitic acid, isocitric acid, α-ketoglutaric acid, succinic acid, fumaric acid, malic acid, oxaloacetic acid, 2-keto-4-hydroxypropanol, 2,4-dihydroxybutanol, 2-keto-4-hydroxybutanol, 2,4-dihydroxybutyric acid, 2-keto-4-hydroxybutyric acid, aspartates, monoalkyl oxaloacetates, dialkyl oxaloacetates, mono- or di-alkyl citrates, aconitates, isocitrates, α-ketoglutarates, succinates, fumarates, malates, oxaloacetates, Vitamin B_1, Vitamin B_2, Vitamin B_6, Vitamin B_{12}, Vitamin C, Vitamin A, Vitamin D, Vitamin E, Vitamin K, Vitamin H, folic acid, pantothenic acids, L-isoleucine, L-leucine, L-

valine, L-lysine, L-methionine, L-phenylalanine, L-threonine, L-tryptophan, L-alanine, L-arginine, L-aspartic acid, L-cysteine, L-glutamic acid, L-histidine, L-proline, L-serine, L-tyrosine, glycine, an inorganic calcium salt, an inorganic sodium salt, an inorganic potassium salt, an inorganic magnesium salt, an inorganic chlorine salt, an inorganic phosphorus salt, an inorganic zinc salt, an inorganic iron salt, an inorganic manganese salt, an inorganic copper salt, an inorganic chromium salt, an inorganic molybdenum salt, an inorganic selenium salt, an inorganic fluorine salt, an inorganic iodine salt, an organic calcium salt, an organic sodium salt, an organic potassium salt, an organic magnesium salt, an organic chlorine salt, an organic phosphorus salt, an organic zinc salt, an organic iron salt, an organic manganese salt, an organic copper salt, an organic chromium salt, an organic molybdenum salt, an organic selenium salt, an organic fluorine salt, and an organic iodine salt.

Present Claims 7-11 and 13 relate to methods for treating the expression of a clinical symptom caused by MELAS, comprising orally administering to a subject in need thereof an effective amount of a composition comprising L-arginine as an active ingredient.

Present Claims 14-18 and 20 relate to methods for treating MELAS, comprising orally administering to a subject in need thereof an effective amount of a composition comprising L-arginine as an active ingredient.

The present inventors have found that the presently claimed compositions and methods are particularly effective for treating the expression of clinical symptoms caused by MELAS and for treating MELAS. The cited references contain no disclosure or suggestion of the presently claimed compositions or methods. Accordingly, these references cannot affect the patentability of the present claims.

The rejection of Claims 1-4 and 6 under 35 U.S.C. § 102(b) in view of U.S. Patent No. 5,543,430 (Kaesemeyer) has been obviated by appropriate amendment. As the Examiner will note, Claim 1 has been amended to include, *inter alia*, the limitations of canceled Claim

5. Applicants respectfully submit that amended Claim 1 is patentable over Kaesemeyer for at least the same reasons Claim 5 was not rejected in view of this reference.

The rejection of Claims 7-10, 12-17, 19, and 20 under 35 U.S.C, § 103(a) in view of U.S. Patent No. 5,891,459 (Cooke et al.) is respectfully traversed. As conceded on page 6 of the Office Action, Cooke et al. does not disclose or suggest any method for treating either the expression of clinical symptoms in a disease caused by MELAS or MELAS itself. The position asserted in the Office Action appears to be that the treatment of such a disease would have been inherent in the method of Cooke et al. However, this position is incorrect. Present Claim 7 recites administering the composition "to a subject in need thereof." The phrase "to a subject in need thereof" clearly refers to the preamble which recites a "method for treating the expression of a clinical symptom caused by MELAS." *See*, *Ex parte Skuballa*, 12 USPQ2d 1570 (PTO BPAI 1989). Thus, Claim 7 and the claims dependent thereon require administration of the composition to a patient suffering from the expression of a clinical symptom caused by MELAS. Similarly, Claim 14 requires administration of the composition to a subject suffering from MELAS. There is no explicit or inherent teaching in Cooke et al. which would suggest selecting the subject subpopulations of Claims 7 or 14. Accordingly, Claims 7 and 14 and the claims dependent thereon are also patentable over this reference.

For these reasons, the rejection should be withdrawn.

The rejection of Claims 1-3 under 35 U.S.C. § 112, first paragraph, for lack of enablement, has been, in part, obviated by appropriate amendment and is, in part respectfully traversed. As the Examiner will note, Claim 1 has been amended to recite that the disease caused by mitochondrial dysfunction is MELAS. Applicants respectfully submit that in view of the teachings in the present specification one of skill in the art could easily determine whether a symptom is caused by MELAS. In further support of this assertion, Applicants direct the Examiner's attention to Y. Koga, et al., "MELAS and L-arginine therapy,"

Mitochondrion, vol. 7, pp. 133-139 (2007) (copy attached as Exhibit A). This publication shows that MELAS is a recognized condition and that one of skill in the art could easily determine whether a symptom was caused by MELAS. Accordingly, the rejection is no longer tenable and should be withdrawn.

The rejection of Claims 5, 11, 12, 18, and 19 under 35 U.S.C. § 112, first paragraph, for lack of written description, has been obviated by appropriate amendment. As the Examiner will note, Applicants have amended the claims to specifically define the another mitochondrial adjuvant. Thus, the rejection should be withdrawn.

Applicants submit that the present application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

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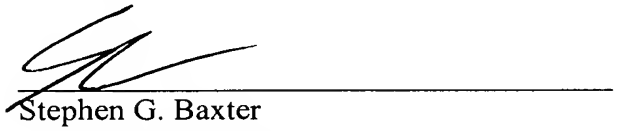

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